CASE REPORT

A SDHB malignant paraganglioma with dramatic response to temozolomide–capecitabine

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Abstract

Ten percent of paragangliomas are malignant and one-third occurs in a genetic background. We report a case of succinate dehydrogenase subunit B (SDHB)-related malignant paraganglioma with dramatic response to temozolomide and capecitabine regimen (decrease in tumor size of 70% with RECIST criteria). Tumor cells harbored a new mutation in *SDHB* gene and showed aberrant hypermethylation of O6-methylguanine-DNA-methyltransferase promoter. Our report suggests the importance of molecular predictive factors of response for the selection of chemotherapeutic as well as targeted agents. This observation points to a possible genotype response to treatment relationships, which could help to design tailor-made treatments in the future.

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Case report

In 1991, a 39-year-old man had a simultaneous diagnosis of retroperitoneal paraganglioma, treated by radical surgery, and macroprolactinoma, treated by transphenoidal surgery, dopaminergic agonists, and radiotherapy. There was no family history suggestive of hereditary endocrine neoplasia including pheochromocytoma, paraganglioma, medullary thyroid cancer, cutaneous lesions, or other endocrine tumor.

In April 2009, 18 years later, at the age of 57, the patient was referred for dyspnea and poor performance status (Eastern Cooperative Oncology Group Performance Status (ECOG) PS = 3). Computed tomography scan showed bilateral mediastinal lymph nodes with tracheal compression associated with two basithoracic lung nodules. Serum chromogranin A levels were 2550 µg/l. Urinary and plasmatic catecholamines were within normal limits. Metaiodobenzylguanidine (MIBG) showed low activity inside the left hilar lymph nodes. In contrast, the ¹⁸FDG-PET scan showed high-grade activity in mediastinal and lung metastases. The histological and immunohistochemical examinations of a mediastinal lymph node biopsy concluded to a metastatic paraganglioma. Ki67 index (MIB-1; Dako, Glostrup, Denmark) was 30%. No staining was observed for O6-methylguanine-DNA-methyltransferase (MGMT)

in the tumor (mouse anti-MGMT MAB, clone MT23.2, Invitrogen Corporation) with positive staining in lymphoid cells as internal positive control (Fig. 1). In our technical conditions, no staining was observed for succinate dehydrogenase subunit B (SDHB; rabbit anti-SDHB polyclonal antibody HPA002868, Sigma–Aldrich Corporation) with positive staining in lymphoid cells as internal positive control (Fig. 2A), while staining was positive in normal adrenal cells, as a control (Fig. 2B). *SDHB* gene mutational analyses demonstrated a novel germline mutation c.412G → A, p.Asp138Asn in exon 4. Aberrant hypermethylation of MGMT promoter was revealed by methylation-specific PCR assay performed on bisulfite-treated DNA.

The patient was successively treated by gemcitabine and oxaliplatin (GEMOX), sunitinib, and temozolomide–capecitabine, using doses previously suggested for neuroendocrine tumors (NETs) (1, 2, 3). Clinical response (improvement of dyspnea, voice, and fatigue), biological response (serum chromogranin A levels), and radiological response (using RECIST criteria) are reported in Fig. 3. First, the patient received eight cycles of gemcitabine (1000 mg/m² i.v.) combined with oxaliplatin (100 mg/m² i.v.) every 14 days; he presented with dramatic clinical improvement after three cycles (ECOG PS = 0), but with grade 2 paresthesia after eight cycles, and partial response rate (17%) using RECIST

Figure 1 MGMT immunohistochemistry: tumor of the patient negative for MGMT with positive staining in lymphoid cells as internal positive control. Original magnification $\times 40$. Full colour version of this figure available via <http://dx.doi.org/10.1530/EJE-11-1098>.

criteria. Two months after the end of GEMOX, clinical and radiological progression occurred. Then, sunitinib (37.5 mg p.o., once daily) was started but stopped after 1 month due to the occurrence of severe hemoptysis treated by arterial embolization; tumor response was not assessed at this time. Lastly, he received eight cycles of capecitabine (750 mg/m² p.o., twice daily, days 1–14) and temozolomide (200 mg/m² p.o., once daily, days 10–14) every 28 days; filgrastim was given to prevent neutropenia (once daily, days 5–10 after each cycle); dramatic objective response rate (70% with RECIST criteria) occurred. The duration of response was 8 months, but capecitabine–temozolomide failed to undergo a new disease control at the time of tumor progression. External radiotherapy of the mediastinum is ongoing.

Figure 2 SDHB immunohistochemistry: tumor of the patient negative for SDHB with positive staining in lymphoid cells as internal positive control (A); striking positive cytoplasmic staining of adrenal cells, as a control (B). Original magnification $\times 10$ (inset $\times 20$). Full colour version of this figure available via <http://dx.doi.org/10.1530/EJE-11-1098>.

Discussion

Paragangliomas are tumors that develop from extra-adrenal chromaffin cells. Approximately 10% of paragangliomas are malignant (4, 5). Until 2002, 10% of pheochromocytoma/paraganglioma were considered to be hereditary. Three possible underlying genetic disorders were identified: multiple endocrine neoplasia type 2 (MEN2), Von-Hippel Lindau (VHL) disease, and neurofibromatose type 1 (NF1). In 2000, mutations in the genes encoding the mitochondrial complex enzyme SDH were discovered (6) and the rate of mutation detection in paragangliomas reached 25–30% (4, 5, 7). New algorithms of genetic testing have been proposed depending on the family/sporadic context, localization of the primary tumor, evidence for bilateral occurrence, biochemical profile of catecholamine secretion, and malignant presentation (4, 8). SDHB mutations were associated with the risk of malignancy and poor prognosis (4, 9), but in contrast with our case, not with tumor response to chemotherapy in preliminary data (10). In our case, SDHB gene was first sequenced because of recurrence of malignant paraganglioma, in a context of negative family history and absence of catecholamine secretion. Indeed, in those patients with malignant disease secondary to an extra-adrenal paraganglioma, almost 50% had SDHB mutations (11). A novel germline mutation, c.412G→A, p. Asp138Asn in exon 4, was identified in our patient. The functional consequences of this mutation were explored by immunostaining of the protein. Loss of expression of SDHB protein was an argument for the loss of wild-type SDHB allele in the tumor, a mechanism already involved in SDHB-related tumors (12, 13).

Surgical resection is considered as the primary treatment when possible. Currently, there is no curative treatment for unresectable malignant paraganglioma. Established treatment modalities include surgery and radionuclide treatment. Chemotherapy is proposed in patients with rapidly progressing tumors and negative MIBG scintigraphy. The optimal systemic treatment for advanced disease is not assessed, due in part to the lack of agents with proven efficacy. The most used regimen combines cyclophosphamide, vincristine, and dacarbazine (CVD) and can provide tumor regression up to 50% (14). Other regimens have been tested, including gemcitabine alone or with docetaxel (15, 16) or paclitaxel (17) and etoposide–cisplatin (18); however, treatment experience with all these regimens is limited and toxicities are severe, whereas quality of life is an important objective in patients whose survival may be long. Sunitinib appears to be a promising treatment in this malignancy based on a few case reports (19, 20). The mechanism of action is similar to that described in other hypoxia-driven tumors and phase II trials are underway (www.clinicaltrials.gov: NCT00843037 and NCT01371201). The other oral drug experiencing some efficacy in this malignancy is

Figure 3 Clinical, biological, and radiological responses of the patient during follow-up. CgA, chromogranin A (reference range, 19.4–98.1 mg/l); GEMOX (gemcitabine and oxaliplatin); Tem–Cap, temozolomide and capecitabine; SD, stable disease; OR, objective response; PD, progressive disease; Clinical res, clinical response. Full colour version of this figure available via <http://dx.doi.org/10.1530/EJE-11-1098>.

temozolomide (21, 22). Temozolomide is a cytotoxic alkylating agent that was initially developed as an oral and less toxic alternative to dacarbazine for patients with metastatic melanoma. Interestingly, in our case, the MGMT promoter hypermethylation was associated with MGMT silencing. MGMT deficiency has been correlated with the response to temozolomide in NETs (23). In patients with glioblastoma, both MGMT promoter methylation and low levels of immunohistochemical MGMT expression have been associated with improved response to temozolomide in most, but not all, studies (24, 25). However, poor correlation in studies directly comparing these two methods has been reported in glioma (26) and no other correlation between MGMT promoter methylation and MGMT deficiency has been reported in NETs. The mechanism of action of temozolomide involves DNA methylation at the O6-guanine site. The methyl group at O6-site is removed by the DNA repair enzyme MGMT. Thereby MGMT protects DNA from methylation damage. Moreover, *in vitro* data indicate that the combination of capecitabine and temozolomide may have a synergistic effect (27). Finally, Strosberg *et al.* (3) recently reported an exceptionally high and durable response rate in a retrospective study of pancreatic NETs with a low rate of toxicity. To our knowledge, we report here the first patient with malignant paraganglioma associated with an impressive clinical and radiological response to this combination. However, temozolomide in paraganglioma has some effect even in monotherapy (21), and a synergistic effect with capecitabine has to be confirmed prospectively. The precise mechanism of this synergism is uncertain; the DNA damage induced by capecitabine may reduce the repair activity of MGMT, thereby potentiating the effect of temozolomide (28). Our report suggests the importance of molecular

predictive factors of response for the selection of chemotherapeutic as well as targeted agents. It prompts to the development of a molecular classification of paragangliomas/pheochromocytomas and to the search for molecular predictive factors in other subtypes of these rare tumors. It may be, for instance, hypothesized that a defect in the VHL pathway or similar pseudohypoxic drive may account for the activity of antiangiogenic treatment as sunitinib in some cases (19).

In conclusion, the synergistic effect of temozolomide and capecitabine ought to be evaluated in metastatic paragangliomas. Our observation needs to be confirmed by prospective studies but already points to possible genotype response to treatment relationships, which could help to design tailor-made treatments.

Declaration of interest

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